REMARKS

Reconsideration of this application is requested.

With entry of this amendment, the pending claims are claims 1 and 4-14.

Claim 1 has been amended to include the features of claims 2 and 3, the latter claims being cancelled, without prejudice, as redundant.

The dependence of claim 4 has been appropriately amended and claim 5 has been amended to depend from both claim 1 and claim 4.

Claim 14 has been amended to include the substance of claim 15.

The amendment of claim 1 is intended to highlight differences between the applicants' invention and the prior art.

It is noted that claims 9, 12 and 15 were only objected to as dependent from a rejected base claim. Claim 9 remains dependent on claim 1 as it is considered that claim 1, as amended, distinguishes patentably over the prior art.

Claim 12 is an independent claim and, therefore, not subject to objection as depending from a rejected base claim. Claim 12 is clearly novel on its own and should be allowable.

As for claim 15, the substance of this claim, as noted, has been added to claim 14. Hence, claim 14, as amended, should be allowable, the subject matter thereof having been recognized as distinguished form the art.

The Examiner is respectfully requested to reconsider the Section 102(b) rejections as set out in ¶s 5, 6 and 7, pages 2-3 of the action. The Examiner's references do not disclose the applicants' invention as defined by the claims herein.

Referring more specifically to the Examiner's Section 102(b) rejections, it is noted that the Examiner has, respectively, rejected claims 1-8, 10, 11, 13 and 14 as anticipated by Hamamoto et al., Chemistry Letters, 1986; claims 1, 2, 7, 8, 10, 11 and 13 as anticipated by JP 62-212395; and claim 14 as anticipated by Wilk et al., Tetrahedron Letters, 2001. However, the references do not disclose the applicants' invention as defined by the rejected claims, particularly as amended.

The applicants attach a copy of an English translation of the cited JP 62-212395 ("Japanese '395") which applicants received on February 21, 2007. The Examiner will note that Japanese '395 mentions the possibility of using toluene as one of a number of possible solvents. However, this indicated use is clearly only speculative as the obviously preferred and only exemplified solvent is ether.

Of the Examiner's references, Hamamoto et al., for example, do not disclose a process as claimed by the applicants including, in particular, the use of the same hydrocarbon solvent for steps (a) and (b). Hamamoto et al., in contrast, only use ether as solvent.

Japanese '395 likewise does not disclose any process including each and every one of the features called for in the applicants' independent claims 1, 12 and 14, e.g. the use of the same hydrocarbon solvent in steps (a) and (b). While Japanese '395 makes a generalized reference to the possibility of using toluene as a solvent, the only exemplification given involves ether as solvent. Hamamoto et al. also only use ether as a solvent, thus, reinforcing the preference of Japanese '395 for the use of this solvent. Clearly, Hamamoto et al., like Japanese '395, does not disclose the applicants' process as called for in the applicants' independent claims.

Finally, Wilk does not disclose any process as claimed by the applicants. It is believed that the Examiner has recognized this as Wilk was only applied against claim 14. Claim 14, as now amended, includes the features of claim 15, which the Examiner only objected to because of its dependence on claim 14. Accordingly, claim 14 should be allowable over Wilk.

It is noted that each of the Examiner's art rejections was made under Section 102(b). Hence, there appears to be no issue of obviousness to discuss. However, for completeness, it is noted that the applicants' process, as defined in the amended claims, would not in any sense be obvious from the Examiner's references. While the applicants acknowledge that Japanese '395 speculates as to the nature of other solvents that might be contemplated for use, it is clear that the preferred solvent of Japanese '395, and the sole solvent exemplified, is ether. This is entirely borne out by the teaching of Hamamoto, where only ether is contemplated. There is nothing in these references, or in Wilk, which would motivate the skilled person to contemplate the processes called for in the claims of the present invention. Further, there is nothing in these references that would cause the skilled person to expect the surprisingly higher yields for the processes of the present invention compared with what is achieved using the preferred solvent of both Japanese '395 and Hamamoto. In this regard, it is noted that the yield quoted in Example 3 of Japanese '395 is 42%. Example 1 of the present application achieves an isolated yield of 53% of the same product produced in Example 3 of Japanese '395. This represents an improvement in yield of over 25% compared with process of Japanese '395.

Furthermore, with regard to the process of applicants' claim 14, it is noted that the yield achieved for the equivalent part of the process in Example 3 of Japanese '395 was 50%. The process of claim 14 exemplified in the present application (step b) achieved a yield of 79%. This demonstrates that the processes of the present invention provide surprisingly higher yields than the process of Japanese '395. In this connection, the Examiner will note that the yield figures quoted are easily calculated from the results given in the examples.

In summary, the applicants submit that their claims define processes which are new and unobvious from the cited art. Accordingly, favorable reconsideration, with allowance, is requested.

Respectfully submitted,

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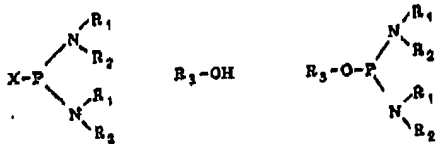
Specification

1. Title of the Invention.

A process for the production of a phosphorus amide compound.

2. Patent Claims

1. A process for the production of a phosphorous amide compound represented by following general formula (III), characterised in that bis amino monohalogenophosphine represented by following general formula (I) is synthesised by reacting trihalogenophosphine and secondary amination agent, and thereafter an alcohol represented by following general formula (II) is reacted.



(I) (II) (III)

(wherein, R_1 and R_2 respectively denote the secondary or tertiary alkyl, or residues which are formed from heterocyclic amine by combining these, X denotes a halogen atom, and R_3 denotes a protecting group of hydroxy group in the phosphoric acid triester).

3. Detailed Description of the Invention.

Sphere of Application in Industry

This invention relates to the following, namely, a process for the production of a phosphorous amide compound, more particularly, relates to a process for synthesising a phosphorous amide compound containing 2 secondary amino groups in a molecule, with good yield.

Technology of the Prior Art

Accompanying with the recent development of genetic engineering, researches have been vigorously carried out on processes to chemically synthesise polynucleotides such as DNA (deoxyribonucleic acid), RNA (ribonucleic acid) and the like that are important materials for genetic engineering.

In the prior art, techniques such as phosphodiester method, phosphoric acid triester method, phosphite method or the like have been known as chemical synthesis methods of polynucleotides. Among these, phosphite method is attracting attention with a point of

reactivity, and in particular, amidite method using phosphoroamidite is attracting attention.

In the said amidite method, chloro-N,N-dialkylaminomethoxy phosphine, chloro-N,N-dialkylaminocyanoethoxy phosphine or the like is generally used as synthesis reagent of nucleotide monomer (for example, Kokai 57-176998, Kohyo 60-502102 or the like), however, the studies so far revealed that there is a difference in stability of the produced nucleotide monomers depending on the substituent species of the secondary amino group, and the ones having branched alkyl group represented by diisopropylamino group and heterocyclic amino group represented by morpholino group are more stable than the ones having straight chain form substituents such as dimethylamino group, diethylamino group or the like (for example, Tetrahedron letters, Vol.24, No.3, pp.245-248, 1983).

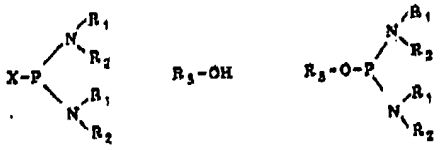
Moreover, among these phosphorus amide compounds, in particular, bis amino-type phosphorus amide compound not including halogen is operationally convenient because halogen atom is not included in the molecule and so hydrogen halide is not co-produced when nucleoside phosphite is synthesised by reacting with nucleoside.

The problems to be solved by Invention

Accordingly, these inventors carried out assiduous investigations in order to develop an efficient process for the production of bis amino-type phosphorus amide compound useful as raw material of DNA synthesis reagent, and as a result, discovered that the process using inexpensive trihalogeno phosphine as a starting material and via bis amino monohalogeno phosphine is superior from the point of reactivity. This invention was completed on the basis of this discovery.

Means to Solve the Problems

Thus, in accordance with this invention, a process for the production of a phosphorous amide compound represented by following general formula (III) is put forward characterised in that bis amino monohalogeno phosphine represented by following general formula (I) is synthesised by reacting trihalogeno phosphine and secondary amination agent, and thereafter an alcohol represented by following general formula (II) is reacted.



[I] [II] [III]

(wherein, R_1 and R_2 respectively denote the secondary or tertiary alkyl, or residues which are formed from heterocyclic amine by combining these, X denotes a halogen atom, and R_3 denotes a protecting group of hydroxy group in the phosphoric acid triester).

In this invention, firstly, bis amino monohalogeno phosphine represented by the aforesaid general formula (I) is synthesised from trihalogeno phosphine and secondary amination agent.

As trihalogeno phosphine to be used, for example, trichloro phosphine, tribromo phosphine or the like are exemplified, and trichloro phosphine is particularly used from an economic point of view.

Moreover, secondary amination agent denotes secondary amine, metallic amide or the like having residue of

(in the formula, R_1 and R_2 are the same as above), and for example, diisopropylamine, di-t-butylamine, morpholine, thiomorpholine, pyrrolidine, piperidine, 2,6-dimethylpyrrolidine, piperazine, trimethylsilyl diisopropylamine, trimethyl silyl di-t-butyl amine, and their lithium amide, sodium amide, aluminum amide or the like may be exemplified.

The reaction of secondary amination agent and trihalogeno phosphine is usually performed in the presence of solvent, and as examples, diethyl ether, tetrahydrofuran, benzene, toluene, xylene or the like may be nominated.

In the reaction, usually about 2 moles of amination agent may be used with respect to 1 mole of trihalogeno phosphine, but a large quantity of amination agent may be present for the purpose of eliminating hydrogen halide co-produced during reaction.

The reaction is carried out usually at a temperature of 0-50°C for about 2-30 hours, however, the reaction is not necessarily restricted to this.

On completion of the reaction, bis amino monohalogeno phosphine is separated from the reaction liquor. The separation means is not limited in particular, but usually it is carried out by distillation. Moreover, when solid halogen acid salt is co-produced in the reaction liquor, separation of solid content by filtration is carried out beforehand. However, in some cases, the subsequent reaction may be carried out without separation of bis amino monohalogeno phosphine from the reaction liquor.

In accordance with this invention, the target phosphorus amide compound represented by the aforesaid general formula (III) can be synthesised by reacting an alcohol represented by the aforesaid general formula (II) to bis amino monohalogeno phosphine obtained in this way.

R_3 in the aforesaid general formula (III) may be any species as long as the it acts as protecting group of hydroxy group when phosphoric acid triester is formed in DNA synthesis, and for example, an alkyl group such as methyl group, ethyl group, propyl group, butyl group or the like, a protecting group which is eliminated by β-cleavage such as β-cyanoethyl group, β-halogenoethyl group, β-nitroethyl group, β-thio cyanoethyl group, β-methylsulfonyl ethyl group, β-phenylsulfonylethyl group or the like, an allyl type protecting group such as allyl group, crotyl group, prenyl group, geranyl group, cinnamyl group, p-chlorocinnamyl group or the like may be exemplified.

Moreover, other examples of these protecting groups and processes for the deprotection are disclosed in detail in Kokai 57-176998, Kohyo 60-502102, Japanese Application No. 60-211240 or the like.

Among these protecting groups, a protecting group which is eliminated by β-cleavage and an allyl type protecting group are preferred from the viewpoint of simplicity of deprotection, prevention of side reaction or the like, and β-cyanoethyl group and an allyl type protecting group of carbon number 6 or less are particularly preferred.

The reaction of alcohol and bis amino mono halogeno phosphine is carried out in a suitable solvent. As examples of solvent, for example diethyl ether, tetrahydrofuran, benzene, toluene, xylene and the like are proposed. When bis amino mono halogeno phosphine is reacted without being isolated, it is desirable to use a common solvent.

Moreover, other reaction conditions may also be suitably selected, and the reaction is usually performed by introducing 1 mole of alcohol with respect to 1 mole of bis amino mono halogeno phosphine, and at 0-50°C for 2-30 hours. Furthermore, a base such as amine or the like is preferably made to co-present in order to eliminate hydrogen halide by-

produced by reaction.

The isolation and purification of product from the reaction liquor can be carried out by suitably selecting well known means of organic synthesis reaction such as distillation, adsorption chromatography, ion exchange chromatography, distribution with organic solvent or the like, or by combining these.

Advantages Afforded by this Invention.

Thus, in accordance with this invention, the target phosphorus amide compound can be obtained efficiently using readily procurable raw materials trihalogeno phosphine, secondary amination agent and alcohol.

On the other hand, by other technique that may be considered where an alcohol is reacted first, it is difficult to obtain monoalkoxy dihalogeno phosphine with good yield, and in addition, it is also difficult to simultaneously introduce 2 secondary amino groups containing bulky substituent, and therefore the target substance cannot be obtained efficiently.

Examples

Below, this invention will be described in greater detail by reference to Examples.

Example 1

In 30 ml ether was dissolved 28.6 mmol phosphorous trichloride, thereafter, 114.4 mmol diisopropylamine was added, and the mixture was stirred at room temperature for 20 hours. On completion of the reaction, the formed diisopropyl ammonium chloride was separated by filtration, then distilled, and an oily bis (N,N-diisopropylamino) chlorophosphine was obtained in a yield of 70 %. Furthermore, this bis (N,N-diisopropyl amino) chlorophosphine 20 mmol was dissolved in 30 ml ether, thereafter, 20 mmol triethylamine and 20 mmol allyl alcohol were added, and the mixture was stirred at room temperature for 15 hours. On completion of the reaction, the formed triethylammonium chloride was separated by filtration, ether was distilled off, then eliminated by distillation, and an oily allyloxy bis (N,N-diisopropylamino) phosphine was obtained. Total yield was 47 %.

- b.p.: 130-133°C/6 mmHg
- ^{1}H NMR(C_6D_6)

1.17 (dd, J = 7.8, 1.8 Hz, 24 H, 4 NCH(CH_3)$_2$), 3.53 (d, sept, J = 10.8, 7.8 Hz, 4 H, 4 NC<u>H</u>), 4.10 (ddt, J = 10.5, 2 Hz, 2 H, C=CCH_2), 5.07 (m, 1H, cis C<u>H</u>=CHCH_2), 5.33 (m, 1H, trans C<u>H</u>=CHCH_2), 5.93 (ddt, J = 18, 10, 5Hz, 1H, CH_2=C<u>H</u>CH_2).

- ^{31}P-NMR (C_6D_6-C_6H_6, 1 : 4) 123.58 ppm.

Example 2

The reaction procedures of Example 1 were repeated under identical conditions except replacing diisopropylamine by morpholine, and allyloxy bis (morpholino) phosphine was obtained. Total yield was 48 mole%.

- b.p.: 145-155°C/0.6 mmHg
- ^{1}H NMR(C_6D_6)

2.90 (qlike $J_{P\text{-}H} = J_{H\text{-}H} = 4.5$Hz, 8H, 4 NCH_2), 3.47 (t, J = 4.5Hz, 8H, 4 OCH_2), 4.10 (m, 2H, C=CCH_2), 5.07 (m, 1H, cis C<u>H</u>=$CHCH_2$), 5.30 (m, 1H, trans C<u>H</u>=$CHCH_2$), 5.88 (ddt, J = 16, 10, 5Hz, 1H, CH_2=C<u>H</u>CH_2).

- ^{31}P-NMR (C_6D_6-C_6H_6, 1 : 4) 130.45 ppm.

Example 3

The reaction procedures of Example 1 were repeated under identical conditions except replacing allyl alcohol by β-cyano ethanol, and β-cyano ethoxy bis (N,N-diisopropylamino) phosphine was obtained. Total yield was 42 mole%.

- b.p.: 123-130°C/0.01 mHg
- ^{31}P-NMR (C_6D_6-C_4H_8O, 1 : 2) 123.85 ppm
- ^{1}H-NMR(CD3Cl)

1.35 (d, 24H 4 $NCH(\underline{CH_3})_2$), 3.82 (m, 4H 4 $N\underline{CH}(CH_3)_2$), 4.03, 4.25 (2 t, 2H -$O\underline{CH_2}CH_2C{\equiv}N$), 2.80 (t, 2H, -$OCH_2\underline{CH_2}C{\equiv}N$).

Comparative Example 1

In 30 ml ether was dissolved 30 mmol phosphorus trichloride, thereafter, 30 mmol β-cyano ethanol and 30 mmol pyridine were added, and the mixture was stirred at room temperature for 20 hours. On completion of the reaction, the formed pyridinium chloride was separated by filtration, then distilled, and an oily β-cyanoethoxy dichloro phosphine was obtained. The yield was approx 15 %.

Thereafter, this 20 mmol β-cyanoethoxy dichloro phosphine was dissolved in 30 ml ether, thereafter, 80 mmol di-isopropylamine was added, and the mixture was stirred at room temperature for 20 hours. However, the target β-cyanoethoxy bis (diisopropylamino) phosphine was hardly obtained.